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Olivier Roy, Sophie Faure, Vincent Thery, C. Didierjean, Claude Taillefumier. Cyclic b-peptoids. Organic Letters, 2008, 10, pp.921-924. hal-00265039

**HAL Id: hal-00265039**

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Submitted on 18 Mar 2008

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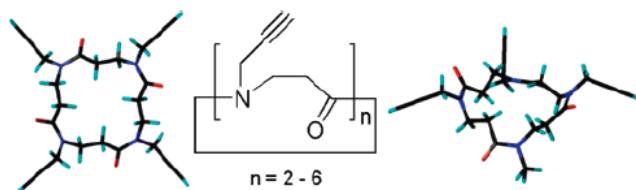
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# Cyclic $\beta$ -Peptoids

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The first synthesis of functionalized  $\beta$ -peptoid macrocycles is reported. X-ray crystallographic structure of tetramer 9 reveals a  $C_2$ -symmetrical derivative with unexpected *all-cis*-amide bonds and spatial disposition of the appendages toward the two opposite faces of the ring. Quantum calculations suggest that 9 is locked in this layout. These macrocycles constitute novel promising templates for multimeric ligation of biologically active ligands. The concept was exemplified by chemical decoration of tetramer 9 via "click" reactions.

The development of oligomers with artificial backbones carrying diverse side chains, capable of mimicking bioactive peptides, is an area of intense research activity.<sup>1</sup> These so-called peptidomimetics can be designed for conformational rigidity of the backbone, their resistance to hydrolytic peptidases and proteases,<sup>2</sup> and their folding properties.<sup>3</sup> Oligoureas,<sup>4</sup> azapeptides,<sup>5</sup> peptoids,<sup>6</sup>  $\gamma$ -peptides,<sup>7</sup> and  $\beta$ -peptides<sup>8</sup> are representative oligomers that belong to this class of peptidomimetic. Among them,  $\beta$ -peptides have been

particularly studied in this regard as  $\beta$ -peptides can adopt a large variety of secondary structures from very short sequences.<sup>9</sup> This unique feature makes them not only interesting oligomers as peptidomimetics but also as foldamers for multimeric attachment of biologically active pharmacophoric groups.<sup>10</sup>  $\beta$ -Peptoids represent a new class

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(1) (a) Barron, A. E.; Zuckermann, R. N. *Curr. Opin. Chem. Biol.* **1999**, *3*, 681–687. (b) Kirshenbaum, K.; Zuckermann, R. N.; Dill, K. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530–535. (c) *Solid-Phase Synthesis*; Kates, S. A., Albericio, F., Eds.; CRC Press: Boca Raton, 2000; pp 649–703.

(2) (a) Frackepohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem* **2001**, *2*, 445–455. (b) Schreiber, J.; Frackepohl, J.; Moser, F.; Fleischmann, T.; Kohler, H. P.; Seebach, D. *ChemBioChem* **2002**, *3*, 424–432.

(3) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180. (b) Price, J. L.; Horne, W. S.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6376–6377.

(4) (a) Hemmerlin, C.; Marraud, M.; Rognan, D.; Graff, R.; Semetey, V.; Briand, J. P.; Guichard, G. *Helv. Chim. Acta* **2002**, *85*, 3692–3711. (b) Violette, A.; Averlant-Petit, M. C.; Semetey, V.; Hemmerlin, C.; Casimir, R.; Graff, R.; Marraud, M.; Briand, J. P.; Rognan, D.; Guichard, G. *J. Am. Chem. Soc.* **2005**, *127*, 2156–2164.

(5) (a) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539–2544. (b) Yoon, J.; Han, H.; Janda, K. D. Solution and soluble polymer syntheses of azatides and aza peptides. *Adv. Amino Acid Mimetics Peptidomimetics* **1999**, *2*, 247–262.

(6) (a) Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H. *J. Am. Chem. Soc.* **1992**, *114*, 10646–10647. (b) Wu, C. W.; Seurynck, S. L.; Lee, K. Y.; Barron, A. E. *Chem. Biol.* **2003**, *10*, 1057–1063. (c) Sanborn, T. J.; Wu, C. W.; Zuckermann, R. N.; Barron, A. E. *Biopolymers* **2002**, *63*, 12–20. (d) Burkoth, T. S.; Fafarman, A. T.; Charych, D. H.; Connolly, M. D.; Zuckermann, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 8841–8845. (e) Fafarman, A. T.; Borbat, P. P.; Freed, J. H.; Kirshenbaum, K. *Chem. Commun.* **2007**, 377–379. (f) Gorske, B. C.; Jewell, S. A.; Guerard, E. J.; Blackwell, H. E. *Org. Lett.* **2005**, *7*, 1521–1524. (g) Kruijtzter, J. A. W.; Hofmeyer, L. J. F.; Heerma, W.; Versluis, C.; Liskamp, R. M. J. *Chem. Eur. J.* **1998**, *4*, 1570–1580.

(7) *Pseudo-Peptides in Drug Discovery*; Nielsen, P. E., Ed.; Wiley-VCH: Weinheim, 2004; pp 33–120.

(8) (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015–2022. (b) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111–1239.

(9) (a) Martinek, T. A.; Fülöp, F. *Eur. J. Biochem.* **2003**, *270*, 3657–3666. (b) Seebach, D.; Hook, D. F.; Glatli, A. *Biopolymers* **2006**, *84*, 23–37.

of synthetic polyamides structurally related to  $\beta$ -peptides in which the amino acid side chain is switched from the C $\alpha$  or C $\beta$  carbon to the amide nitrogen. Since the concept was introduced by Hamper<sup>11</sup> in 1998, very few reports have concerned this class of compounds,<sup>12</sup> and to date, their cyclic counterparts have not been investigated at all. Interesting biological properties are associated to cyclo  $\beta$ -peptides;<sup>13</sup> however, the poor solubility encountered with  $\beta$ -peptides<sup>13a</sup> may hamper their cyclization. It is expected that the lack of hydrogen on the amide can greatly modify the physical as well the folding properties of  $\beta$ -peptoids related to  $\beta$ -peptides.<sup>14</sup> Cyclization of molecules containing tertiary amide is often facilitated due to the easy trans–cis isomerization of the amide bond.<sup>15</sup> With all these considerations in mind, we therefore decided to investigate the synthesis and further cyclization of short functionalized  $\beta$ -peptoids. To the best of our knowledge, cyclic  $\beta$ -peptoids have never been reported, and therefore, conformational aspects including the general shape of such macrocycles, cisoid/transoid geometry of the amide bonds, the relative orientation of the CO as well as orientation of the appendages on the backbone merit investigation.

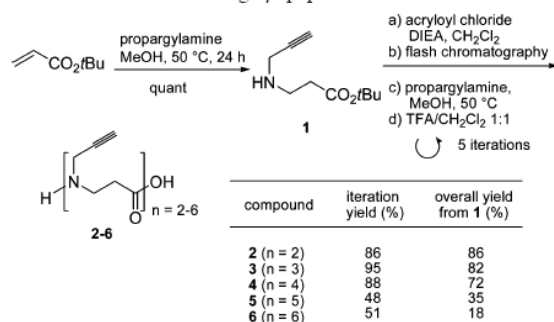
Since the final objective of our work was to ligate the template to key elements like carbohydrate for multimeric recognition events, we decided first to anchor cyclo- $\beta$ -peptoids with terminal alkyne groups ready for click chemistry approach.

As indicated by recent studies, the most convenient route to  $\beta$ -peptoids is a two-step iterative methodology involving acryloyl chloride as acylating agent for amide bond formation and aza-Michael addition of primary amines to the resulting  $\alpha,\beta$ -unsaturated amide. Repeating this chemistry for several cycles allows the synthesis of  $\beta$ -peptoid oligomers. This methodology is also convenient in solid-phase organic synthesis (SPOS); this is of great interest in case of combinatorial approaches, but it is limited to small quantities, yields seem to be affected after five to six repetitive cycles,<sup>12b</sup> and byproducts corresponding to shorter and/or longer oligomers have also been isolated.<sup>14a</sup> Therefore, we found it more convenient to conduct solution-phase synthesis, although some purification steps were expected.

*N*-Propargyl-functionalized  $\beta$ -alanine **1**, the key building block for the synthesis of the expected short  $\beta$ -peptoids

oligomers, was prepared quantitatively on a gram-scale (Supporting Information). From this monomer, elongation according to a two-step iterative procedure (acylation with acryloyl chloride followed by 1,4-addition with the appropriate amine) allowed the facile preparation of varying chain length oligomers **2–6** depending on the number of cycles (Scheme 1). Each two-step elongation required one purifica-

**Scheme 1.** Iterative Solution-Phase Synthesis of Oligo- $\beta$ -peptoids



tion stage and furnished the  $n + 1$  oligomer with yields ranging from 86 to 48%. After each cycle, a portion was deprotected (TFA) for cyclization reaction.

Macrocyclization study started with the medium size linear tetramer **4** using *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) and diphenylphosphoryl azide (DPPA) acylating agents at moderate dilution (5–10 mM). All experimental conditions (entries 8–12, Table 1) successfully furnished the expected cyclotetramer **9** in good isolated yields (flash chromatography, SiO<sub>2</sub>) ranging from 48 to 65%. Cyclization of **4** to 16-membered macrocycle **9** appears to be not very sensitive to the conditions, indicating a favorable process. Liquid chromatography/mass spectrometry (LC/MS) of the crude showed that formation of cyclotetramer **9** was only contaminated by trace amount of a cyclic homodimer compound (<1%, estimated by RP-HPLC at 214 nm). Pentamer **5** and hexamer **6** were also converted to the corresponding macrocycles **10** and **11** in good isolated yields, 67 and 68%, respectively, with DPPA in acetonitrile (entries 14 and 16). LC/MS profiles of the crude products allowed the detection of cyclodimeric compounds; further estimated by RP-HPLC in a range of 1–2%. Difficulties are often encountered with the cyclization of short oligomers due to ring strain. Cyclization of trimer **3** supposed to form the 12-membered ring **8** was assessed under a set of conditions (entries 3–7, Table 1). Whatever the coupling reagent and conditions, an inseparable mixture of **8** and cyclodimeric product **11**, having a 24-membered ring was formed. HATU proved to be the more efficient reagent, while benzotriazolylxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) used by others<sup>15</sup> for cyclization of peptoids (poly-*N*-substituted glycine) was in our hand deleterious. As anticipated, cyclization of dimer **2** proved challenging. The expected cyclic

(10) (a) Norgren, A. S.; Arvidsson, P. I. *Org. Biomol. Chem.* **2005**, *3*, 1359–1361. (b) Simpson, G. L.; Gordon, A. H.; Lindsay, D. M.; Promsawan, N.; Crump, M. P.; Mulholland, K.; Hayter, B. R.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 10638–10639.

(11) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. *J. Org. Chem.* **1998**, *63*, 708–718.

(12) (a) Mejias, X.; Feliu, L.; Planas, M.; Bardaji, E. *Tetrahedron Lett.* **2006**, *47*, 8069–8071. (b) Shuey, S. W.; Delaney, W. J.; Shah, M. C.; Scialdone, M. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1245–1248. (c) Olsen, C. A.; Bonke, G.; Vedel, L.; Adersen, A.; Witt, M.; Franzyk, H.; Jaroszewski, J. W. *Org. Lett.* **2007**, *9*, 1549–1552.

(13) (a) Gademann, K.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 2924–2937. (b) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1223–1226. (c) Gademann, K.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 957–962.

(14) (a) Norgren, A. S.; Zhang, S.; Arvidsson, P. I. *Org. Lett.* **2006**, *8*, 4533–4536. (b) Baldauf, C.; Günther, R.; Hofmann, H.-J. *Phys. Biol.* **2006**, *3*, S1–S9.

(15) Shin, S. B.; Yoo, B.; Todaro, L. J.; Kirshenbaum, K. *J. Am. Chem. Soc.* **2007**, *129*, 3218–3225.



**Table 1.** Macrocyclization of Linear  $\beta$ -Peptoids 2–6

entry	conditions	compd		yield <sup>a</sup> (%)
		linear	cyclic	
1	HATU (1.2 equiv), DIEA (2 equiv), CH <sub>2</sub> Cl <sub>2</sub> /DMF 4:1 (5 mM)	2	7/9	16/12 <sup>b</sup>
2	DPPA (2 equiv), DIEA (3 equiv), CH <sub>3</sub> CN (5 mM)	2	7/9	26
3	HATU (1.2 equiv), DIEA (2 equiv), CH <sub>2</sub> Cl <sub>2</sub> + $\epsilon$ DMF (10 mM)	3	8/11	69 <sup>c</sup>
4	DPPA (1.5 equiv), NaHCO <sub>3</sub> (9 equiv), DMF (10 mM)	3	8/11	30 <sup>c</sup>
5	DPPA (2 equiv), DIEA (3 equiv), DMF (10 mM)	3	8/11	27 <sup>c</sup>
6	DPPA (2 equiv), DIEA (3 equiv), CH <sub>3</sub> CN (5 mM)	3	8/11	66 <sup>c</sup>
7	PyBOP (2 equiv), DIEA (3 equiv), CH <sub>2</sub> Cl <sub>2</sub> (5 mM)	3	8/11	<sup>d</sup>
8	HATU (1.2 equiv), DIEA (2 equiv), CH <sub>2</sub> Cl <sub>2</sub> /DMF 4:1 (10 mM)	4	9	57
9	DPPA (2 equiv), NaHCO <sub>3</sub> (9 equiv), CH <sub>3</sub> CN/DMF 8:2 (10 mM)	4	9	48
10	DPPA (2 equiv), NaHCO <sub>3</sub> (9 equiv), CH <sub>3</sub> CN/DMF 9:1 (5 mM)	4	9	65
11	DPPA (2 equiv), DIEA (3 equiv), CH <sub>3</sub> CN (10 mM)	4	9	63
12	DPPA (2 equiv), DIEA (3 equiv), CH <sub>3</sub> CN (5 mM)	4	9	55
13	HATU (1.2 equiv), DIEA (2 equiv), CH <sub>2</sub> Cl <sub>2</sub> /DMF 4:1 (5 mM)	5	10	52
14	DPPA (2 equiv), DIEA (3 equiv), CH <sub>3</sub> CN (5 mM)	5	10	67
15	HATU (1.2 equiv), DIEA (2 equiv), CH <sub>2</sub> Cl <sub>2</sub> /DMF 4:1 (5 mM)	6	11	59
16	DPPA (2 equiv), DIEA (3 equiv), CH <sub>3</sub> CN (5 mM)	6	11	68

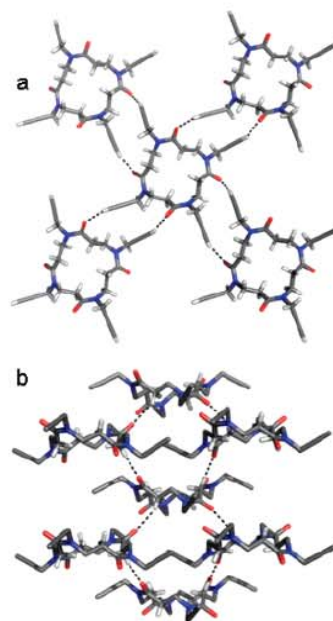
<sup>a</sup> Yield of pure isolated products. <sup>b</sup> Not separated. <sup>c</sup> Inseparable mixture by silica gel chromatography. <sup>d</sup> No reaction.

dipeptoid 7 was isolated as a pure compound in low yield (16%) beside cyclotetramer 9 (12%) (entry 1).

Colorless prismatic crystals suitable for X-ray structure analysis of tetramer 9 were grown by slow evaporation from deuterated methanol solution at room temperature. The crystal structure of 9, the first to be solved for a cyclic  $\beta$ -peptoid compound, adopts a  $C_2$ -symmetrical nonplanar square-shaped conformation with dimensions  $4.89 \times 4.89$  Å. All amide bonds are in the *cis* configuration, in sharp contrast with the solid-state structure of known cyclo- $\beta$ -tetrapeptides which have all the peptide bonds in *trans* geometry.<sup>16</sup> In the field of peptoids, a leading publication from Kirshenbaum et al.<sup>15</sup> reports on cyclic  $\alpha$ -peptoids containing *cis*- and *trans*-amides; however, to the best of

our knowledge, structure 9 is the first macrocyclic oligoamide containing only *cis*-amide bonds. All four carbonyl groups are directed outside of the ring and make two subsequent angles of  $54^\circ$  and  $126^\circ$  with the vertical 2-fold symmetry axis. This is also a major difference with previous work on cyclo- $\beta$ -peptides describing a unidirectional arrangement of the amides with NH and C=O groups oriented to opposite faces of the peptide ring, perpendicularly to the ring. As a consequence, cyclic  $\beta$ -peptides are known to form unique nanotube assemblies<sup>17</sup> due to supramolecular staking mediated by intermolecular hydrogen-bonding both in the solid state and in solution.

The crystal packing can be described as layers of molecules perpendicular to the 2-fold symmetry axis (Figure 1a) and as column of molecules along the  $C_2$  axis (Figure



**Figure 1.** Crystal structure of 9: (a) four cyclic subunits in one layer showing the formation of the 18-membered pseudorings, (b) column-like crystal packing and interlayer stabilization via CH $\cdots$ O interactions. The intermolecular interactions are shown as dashed lines.

1b). The molecules in a layer are held together via intermolecular CH $\cdots$ O hydrogen bonds<sup>18</sup> involving carbonyl groups and acetylenic H atoms ( $D = 3.223$  Å,  $d = 2.34$  Å,

- (16) (a) Seebach, D.; Matthews, J. L.; Meden, A.; Wessels, T.; Baerlocher, C.; McCusker, L. B. *Helv. Chim. Acta* **1997**, *80*, 173–182. (b) Sutton, Peter, W.; Bradley, A.; Elsegood, M. R. J.; Farràs, J.; Jackson, R. F. W.; Romea, P.; Urf, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 2629–2632. (c) Buttner, F.; Norgren, A. S.; Zhang, S.; Prabpai, S.; Kongsaree, P.; Arvidsson, P. I. *Chem. Eur. J.* **2005**, *11*, 6145–6158. (17) (a) Tereshko, V.; Monserrat, J. M.; Pérez-Folch, J.; Aymami, J.; Fita, I.; Subirana, J. A. *Acta Crystallogr.* **1994**, *B50*, 243–251. (b) Clark, T. D.; Buehler, L. K.; Ghadiri, R. J. *Am. Chem. Soc.* **1998**, *120*, 651–656. (18) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, U.K., 1999.

$\theta = 159^\circ$ ), leading to the formation of 18-membered pseudorings. Interlayer  $\text{CH}\cdots\text{O}$  interactions were also observed between the carbonyl and the methylene groups of the cyclic  $\beta$ -peptoid ( $D = 3.485 \text{ \AA}$ ,  $d = 2.57 \text{ \AA}$ ,  $\theta = 157^\circ$ ). It should also be noted that two propargyl groups are pointing toward one face and the other two toward the opposite face in an alternative manner. That is a very interesting feature considering the design of well-defined template for multivalent ligands anchoring.<sup>19</sup>

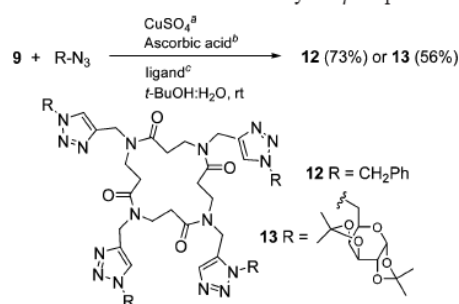
Due to a small energy difference between cis and trans tertiary amide bonds, linear peptoids **2–6** were observed as mixtures of cis/trans configurational isomers.<sup>20</sup> However, both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectrum of **9** were very simple, showing only one resonance for each kind of proton and carbon, in agreement with a symmetrical structure. Thus, only one configurational isomer exists in solution, tentatively assigned to the all-cis isomer found in the solid. For that purpose the all-cis cyclic tetramer **9** was sampled by simulating annealing method and the energetically most favorable structure was optimized at the DFT (B3LYP/6-31G\*\*) level. Geometry optimization was also performed with an all-trans and an alternate cis–trans arrangement, both in agreement with NMR data, and the thermodynamic properties were evaluated. According to DFT calculations, the all-trans cyclic tetramer is 7.3 kcal more stable than the isolated all-cis compound and 4.7 kcal more stable than the alternate cis–trans structure. From these results, one can roughly estimate that for each amide bond in the ring, the cis configuration, compared to the trans, is disfavored by about  $2 \text{ kcal}\cdot\text{mol}^{-1}$ , in the order of what is known for secondary amide bonds.<sup>21</sup>

Since large  $\Delta(\Delta G)$  are measured between the three putative symmetrical arrangements, one can reasonably assume that the all-cis configurational isomer is the primary product from macrocyclization; i.e., it does not arise from the equilibration of a more stable isomer during crystallization. These results would suggest that the all-cis compound exists both in the solid and in solution. The kinetic all-cis compound is likely obtained, from an all-cis open-chain isomer, displaying the most favorable conformation for cyclization. At the moment, no suitable crystals have been obtained to perform X-ray diffraction studies of cyclic pentamer **10** and hexamer **11**. However, their NMR spectra are very instructive. The magnetic equivalence of the different protons and carbons of all five residues in **10** ( $\text{DMSO}-d_6$ ) clearly indicates that **10** possesses a 5-fold molecular symmetry. This symmetry implies that the 20-membered ring should possess only one type of amide bonds, cis or trans and that all the side chains should point toward the same face of the ring. In the case of hexamer **11**, the

spectra complexity ( $^1\text{H}$  and  $^{13}\text{C}$ ), comparable to those of linear peptoids is likely due to cis–trans isomerizations, a characteristic that, in addition to a large size of the ring increases its conformational flexibility.

Cyclic  $\beta$ -peptoids have been prepared as new promising template for multimeric bioactive ligands anchoring. We chose to synthesize compounds **12** and **13** to demonstrate proof of principle for the efficient functionalization of these macrocycles using click chemistry.<sup>22</sup> Conjugation was achieved by reacting **9** with benzyl azide or 6-deoxy-6-azido-1,2–3,4-diisopropylidene  $\alpha$ -D-galactopyranose in the presence of  $\text{CuSO}_4$ , ascorbic acid, and tris(benzyltriazolylmethyl)amine (TBTA) as a ligand or a hydrosoluble analogue (Scheme 2).<sup>23</sup>

**Scheme 2.** Functionalized Cyclic  $\beta$ -Peptoids



<sup>a</sup> 4 mol % for **12**, 8 mol % for **13**. <sup>b</sup> 12 mol % for **12**, 24 mol % for **13**. <sup>c</sup> 4 mol % of TBTA for **12**, 8 mol % of hydrosoluble TBTA for **13** (see the Supporting Information).

In summary, we have described the first macrocyclization study of  $\beta$ -peptoids. Functionalization of tetramer **9** was addressed via “click” reactions. X-ray analysis of tetramer **9** has revealed an unprecedented all-cis cyclic structure. For cyclic  $\beta$ -peptoids larger than a 20-membered ring, it is likely that the conformational behavior of  $\beta$ -peptoids macrocycles depends on cis–trans isomerizations.

**Acknowledgment.** We thank Bertrand Legeret (Université Blaise Pascal - Clermont-Ferrand II) for LC–MS analysis and HRMS measurements

**Supporting Information Available:** Experimental details, characterization of new compounds, X-ray crystallography data for **9**, RP-HPLC data, NMR spectra, and total energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(19) Boturyn, D.; Coll, J. C.; Garanger, E.; Favrot, M. C.; Dumy, P. *J. Am. Chem. Soc.* **2004**, *126*, 5730–5739.

(20) Linear peptoids with cis amide bonds have been repeatedly described, see for example the following reference describing a pentamer with all-cis-amide bonds: Armand, P.; Kirshenbaum, K.; Goldsmith, R. A.; Farr-Jones, S.; Barron, A. E.; Truong, K. T. V.; Dill, K. A.; Mierke, D. F.; Cohen, F. E.; Zuckermann, R. N.; Bradley, E. K. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4309–4314.

(21) Poteau, R.; Trinquier, G. *J. Am. Chem. Soc.* **2005**, *127*, 13875–13889 and references cited therein.

(22) Jang, H.; Fafarman, A.; Holub, J. M.; Kirshenbaum, K. *Org. Lett.* **2005**, *7*, 1951–1954. Holub, J. M.; Jang, H.; Kirshenbaum, K. *Org. Biomol. Chem.* **2006**, *4*, 1497–1502.

(23) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853–2855.